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ORIGINAL ARTICLE

Prevalence of preclinical renal dysfunction in obese Egyptian patients with primary knee osteoarthritis, preliminary data

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KEYWORDS

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Abstract *Aim of the work:* Obesity and the related metabolic syndrome cluster of cardiovascular risk factors have been associated with chronic kidney disease (CKD). Patients with knee osteoarthritis (OA) are frequently obese and due to the combined effects of obesity and the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs); they may represent a high risk group for renal dysfunction. We aimed to detect preclinical renal involvement in obese patients with knee OA.

Patients and methods: Forty patients with knee OA and a body mass index (BMI) $\geqslant$ 30 (mean age 43.5 $\pm$ 3.7 years) not on chronic NSAID use and forty age and sex matched non-obese controls were enrolled in this study. For all subjects anthropometric measures were taken. Laboratory assessment included fasting blood sugar, serum triglycerides, high density lipoprotein cholesterol (HDL), serum uric acid, urea, creatinine and microalbuminuria assay. For patients with knee OA, knee radiographs were done and the disease severity was assessed according to Kellgren–Lawrence (K–L) scale. Tc-99 m DTPA was used for the measurement of the glomerular filtration rate (GFR) and the results were classified into normal and CKD according to Kidney–Dialysis Outcomes and Quality Initiative stages.

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Results: Among the patients' group, 26/40 (65%) had CKD compared to 12/40 (30%) subjects among the controls ($P = 0.001$). GFR correlated positively with HDL ($r = 0.4$; $P = 0.02$) and inversely with microalbuminuria and the severity of knee OA ($r = -0.4$; $P = 0.02$ for each).

Conclusions: Obese patients with knee OA represent a high risk group for renal dysfunction.

1. Introduction

Obesity represents one of the most important global public health issues which because of its rapidly increasing prevalence and association with a wide range of diseases warrants increased attention by physicians and other health care professionals [1]. Obesity is defined by a body mass index (BMI) $\geqslant 30$ kg/m^2 [2], while other anthropometric measures that reflect abdominal obesity or central obesity include the waist circumference (WC), the waist/hip ratio (WHR) and waist/height ratio (WHtR) [3,4]. Central obesity has been found to be more related to the metabolic syndrome (MetS) cluster of cardiovascular risk factors (including central obesity, hypertension, dyslipidemia and hyperglycemia) than the BMI [5]. Although anthropometric indicators such as BMI, WC, WHR, and WHtR have been traditionally used to predict MetS and associated chronic diseases, there is controversy in the literature as to which measure of obesity is best related to cardiovascular risk factors [4].

Obese patients have an increased prevalence of major comorbidities including cardiovascular disease, hypertension, diabetes mellitus and risk factors for chronic kidney disease (CKD) [6]. In fact, excess body weight has been identified as a major risk factor for the development of CKD and end stage renal disease (ESRD) by itself, independent of blood pressure levels, and the presence of diabetes significantly increases such a risk [7]. On the other hand, several studies have shown that even modest impairment in renal function may be an independent predictor of cardiovascular morbidity and mortality [8–10]. Furthermore, microalbuminuria has been found to be a strong, consistent and independent predictor of all-cause and cardiovascular mortality and morbidity in individuals with and without diabetes [11].

Population-based studies of osteoarthritis [OA] have consistently shown that overweight people are at higher risk of developing knee OA than non-over weight controls [12,13]. Obese women [BMI $>$ 30; yet $\leqslant$ 35] had almost four times risk of OA as women whose BMI was under 25. For men in the same weight category; the risk was increased 4.8-fold over normal weight men [13]. There is growing evidence that osteoarthritis is not simply a disease related to aging or mechanical stress on the joints but rather a "metabolic disorder" in which various interrelated lipid, metabolic and humoral mediators contribute to the initiation and progression of the disease process [14]. In the Japanese Research on Osteoarthritis against Disability (ROAD), the odds of OA increased with the presence of each additional component of the metabolic syndrome [15]. Similarly, in the Michigan Bone Health and Metabolism Study, in obese women, the presence of two or more cardiometabolic risk factors was associated with more reports of persistent knee pain over the previous 3 years [16]. Patients with OA frequently use nonsteroidal anti-inflammatory drugs [NSAIDs] for pain relief, and since these drugs may adversely affect renal function especially in the elderly with pre-existing renal disease, hypertension, heart failure, or those concomitantly treated with anti- hypertensive agents [17], obese patients with OA due to the combined effects of obesity, MetS and the side effects of NSAIDs may represent a high risk group for renal dysfunction. Indeed, besides other risk factors for cardiovascular disease, OA patients have been found to have a high prevalence of renal impairment [18].

Although in routine clinical practice serum creatinine is used to assess renal function; it is inaccurate if used without a correction factor for sex, age and muscle mass. Besides, isolated reduced glomerular filtration rate (GFR) can be present despite normal serum creatinine which may not be elevated until the GFR is less than 30–50% of normal [19]." The cornerstone for diagnosing renal disease is GFR which is influenced by various factors including structural and/or functional kidney disease as well as patient's age, weight, and body surface area. The gold standard for GFR estimation is inulin clearance, which requires a steady-state plasma concentration and urine collection but is too costly and time-consuming. In routine clinical practice, chromium-51-ethylenediaminetetraacetic acid clearance is a widely accepted and accurate substitute yet a very expensive screening tool [10,20]. Subsequently, other isotope clearance methods have been validated, employing labeled iodothalamate and diethylenetriamine pentaacetic acid (DTPA) [21]. We aimed to measure the GFR in obese patients with primary knee osteoarthritis and normal serum creatinine not on chronic NSAID use to detect subclinical renal affection in this high risk group for renal dysfunction and establish relations between obesity, metabolic risk factors and glomerular function.

2. Patients and methods

The study was a cross-sectional case-control study and was approved by the local ethics committee of the Cairo University scientific review board. Informed consent was obtained from all subjects according to the Declaration of Helsinki; General Assembly, October 2008. The study was conducted on 40 patients with primary knee OA and a BMI $\geqslant 30$ kg/m^2 (G1). They were 35 females and 5 males with a mean age of (43.5 $\pm$ 3.7 years). Knee OA was diagnosed according to the American College of Rheumatology (ACR) criteria for knee OA [22]. Forty age and sex matched non-obese healthy subjects were included and served as a control group (G2). Patients and controls were recruited from the Rheumatology Department, Cairo University hospitals. Patients with elevated serum creatinine (>1.2 mg/dl), diabetes (fasting blood sugar $\geqslant 126$ mg/dl), evidences of urinary tract infection, hypertension (defined as blood pressure $\geqslant 140/90$ mmHg and/or use of antihypertensive drugs) or other cardiovascular diseases, abnormal renal sonography or on chronic use of NSAIDs were

excluded from the study. Patients who only used NSAIDs occasionally were not excluded.

All patients and controls were subjected to full history taking and clinical examination including measurement of blood pressure (BP), weight, height, WC, WHR, WHtR and articular examination. WHR was considered increased if $\geqslant 0.9$ in men and $\geqslant 0.85$ in women [3] and the cut-point for WHtR was 0.5 for both genders [23].The severity of knee OA on anteroposterior knee radiographs was assessed according to the Kellgren/Lawrence (K–L) grading system [24]. The disease duration was calculated from the onset of knee pain in months.

BMI was calculated for all subjects. Biochemical analyses were done after overnight fasting and included fasting blood sugar (FBS), high density lipoprotein cholesterol (HDL), triglycerides (TG), urea, creatinine and uric acid. The normal laboratory reference ranges for serum urea, creatinine and uric acid were 7–21, 0.4–1.2 and 2.5–6.8 mg/dl, respectively. Microalbuminuria assay was done by competitive enzyme immunoassay, using IMMULITE-2000 apparatus and albumin kits [25]. Microalbuminuria is defined as a urinary albumin concentration of 20–200 mg/l while urinary albumin concentration >200 mg/l is considered macroalbuminuria [26]. MetS was diagnosed when three or more of the following risk factors were present: WC >88 cm in women and >102 cm in men, TGs $\geqslant 150$ mg/dl, HDL <40 mg/dl in males and <50 mg/dl in females, BP $\geqslant 130/85$ mmHg, FBS $\geqslant 110$ mg/dl according to the National Cholesterol Education Program-Adult Treatment Panel (NCEP) criteria [27].

All subjects maintained their usual diet, but were recommended to avoid excessive dietary intake of protein or salt 10 days before GFR measurement. Absolute GFR [not the corrected] was measured using Tc-99 m DTPA; Gates' method [28]. Proper hydration was ensured, followed by intravenous infusion of five mCi of Tc-99 m DTPA, then serial posterior dynamic frames were acquired for 6 min. DTPA is taken up by the kidney through glomerular filtration and is not secreted or reabsorbed by the renal tubules. Once it reaches the kidney, about 20% is accumulated, and the remainder flows away; a value approximating the filtration fraction. Patients' categorization was performed according to the recommendations of Kidney–Dialysis Outcomes and Quality Initiative (K/DOQI) [29] using GFR. Stage I represents patients with normal GFR $\geqslant 90$ ml/min with kidney damage as manifested by abnormalities noted on renal pathology, blood, urine or imaging tests while stage II–V represent those with CKD.

All statistical calculations were done using computer program SPSS version-15 for Microsoft Windows. Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Spearman's rank correlation equation. Linear annual reduction in GFR was calculated in knee OA patients. *P* values less than 0.05 were considered statistically significant.

3. Results

This study included 40 obese patients with primary knee OA (age range 40–52; mean 43.5 ± 3.7 years) including 35 females and 5 males, classified as G1. Thirty patients did not use NSAIDs, while 10 others used NSAIDs on intermittent basis one to three times/week. The means of BMI and disease duration of G1 were 37.28 ± 5.9 (range; 30–50 kg/m^2) and 20.2 ± 14.7 (range; 3–25 months) respectively. According to K–L grading system for radiographic severity of OA; we found 4 (10%), 20 (50%), 14 (35%) and 2 (5%) belonging to grades 1, 2, 3 and 4 respectively. Thirty-nine (97.5%) OA patients were found to have MetS. The last patient had abdominal obesity and a low HDL level but did not fulfill the criteria for the diagnosis of MetS. Forty age (44.4 ± 3.9 years) and sex (35 females and 5 males) matched, non-obese subjects served as a control group with BMI of 23.5 ± 1.3 (range; 19–25 kg/m^2) and were classified as G2. The different clinical and physical parameters of both groups are shown in Table 1. BMI, WC, WHR and WHtR were significantly higher in G1 than in G2 ($P = 0.000$) while there was no statistical difference in systolic or diastolic blood pressures between both groups.

The laboratory data and GFR are detailed in Table 2. FBS, uric acid, TG, and microalbuminuria were significantly higher in G1 ($P = 0.004, 0.000, 0.000, 0.008$, respectively) while HDL was significantly lower ($P = 0.000$) than in G2. Among G1,

Table 1 Clinical and physical parameters in patients and controls.

	Patients (G1)	Patients (G2)	*P*-value
Age (years)	43.5 ± 3.7	44.4 ± 3.9	0.9
Sex distribution			–
Females	35 (87.5%)	35 (87.5%)	
Males	5 (12.5%)	5 (12.5%)	
WC (cm)	116.9 ± 15	77 ± 5.2	0.000
WHR	1 ± 0.1	0.8 ± 0.1	0.000
WHtR	0.7 ± 0.1	0.5 ± 0.02	0.000
BMI	37.28 ± 5.9	23.5 ± 1.3	0.000
SBP (mm Hg)	115.9 ± 13.1	112.4 ± 10.3	0.8
DBP (mm Hg)	74.4 ± 11	71.8 ± 9.3	0.9

G1, group 1; G2, group 2; WC, Waist circumference; WHR, waist-hip ratio; WHtR, waist-height ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are expressed as mean ± SD or no (%).

Table 2 Laboratory data and glomerular filtration rate of the study groups.

	Patients (G1)	Control (G2)	*P*-value
FBS (mg %)	102 ± 12.7	93.7 ± 12	0.004
Creatinine (mg/dl)	0.6 ± 0.1	0.6 ± 0.1	0.9
Urea (mg/dl)	11.4 ± 3.6	12.5 ± 4	0.9
Uric acid (mg/dl)	4.3 ± 0.9	3.5 ± 0.8	0.000
TG (mg/dl)	439.4 ± 190.5	150 ± 31	0.000
HDL (mg/dl)	33.3 ± 7.7	48 ± 0.8	0.000
Microalbuminuria (mg/l)	37.2 ± 4	17 ± 5	0.008
GFR (ml/min)	82.8 ± 17.8	94.2 ± 10.3	0.001
	Range (32–120)	Range (82–120)	
MS (No. %)	39/40 (97.5%)	0	0.000

FBS, fasting blood sugar; TG, Triglycerides; HDL, high density lipoprotein; GFR, glomerular filtration rate; MS, metabolic syndrome. Values are expressed as mean ± SD unless otherwise specified.

Table 3 Categorization of patients and controls based on K/DOQI staging system.

	Patients (G1)	Control (G2)	*P*-value
Entirely normal	14 (35%)	28 (70%)	0.01
K/DOQI Staging			
Stage I	0	0	–
Stage II	22 (55%)	12 (30%)	0.01
Stage III	4 (10%)	0	0.01
Stage IV and V	0	0	–

97.5% fulfilled the criteria for the metabolic syndrome versus none in G2 ($P = 0.000$). Serum urea and creatinine were not significantly different between both groups, however G1 patients had significantly lower mean GFR in comparison to G2 ($P = 0.001$).

Patients' categorization into normal and chronic kidney disease (CKD) using GFR is shown in Table 3. 26/40 (65%) were positive for CKD in G1 compared to 12/40 (30%) in G2 ($P < 0.01$). Calculated annual reduction in GFR in G1 was 1.65 ± 0.2 ml/min/1.73 m^2/year.

Correlations were done between the different physical, clinical, laboratory and radiological parameters in G1 with GFR. There was a significantly positive correlation with HDL ($P = 0.002$) and a significantly negative correlation with microalbuminuria and K–L grade of OA severity ($P = 0.003$ for both). None of the parameters showed significant correlation in the control group (G2). Regarding microalbuminuria, statistically significant positive correlations were found with disease duration, WHtR, BMI and K–L grade ($P = 0.02$, 0.03 and 0.03, 0.01, respectively) and a statistically significant negative correlation was found with HDL ($P = 0.02$) Finally, K–L grade for OA severity showed statistically significant positive correlation with disease duration, WC, WHtR, BMI ($P = 0.001$, 0.005, 0.004, 0.001, respectively, as well as a significantly negative correlation with HDL ($P = 0.02$). All correlations are detailed in Table 4.

4. Discussion

This study showed that obese patients with knee OA represent a high risk group for renal dysfunction. The mean GFR in OA patients was significantly lower compared to the control group ($P = 0.001$) with 65% of OA patients having CKD versus 30% of the control group.

Consistent with previous reports on the association of obesity with knee OA [12,13]; in this study, the severity of OA as assessed by the K–L grade was significantly positively correlated with BMI, WC and WHtR. Expectedly, a significantly positive correlation was found between the disease duration and K–L grade (r 0. 8, $P = 0.001$).

In a population based study in the United States, MetS was seen in 59% of the population with OA compared to 23% in the non OA population. The association between MetS and OA was strongest in the younger population and diminished with increasing age; having OA at a mean age of 43.8 years was associated with a 5.26-fold increased risk of having MetS [30]. In the present study, 97.5% of patients with knee OA fulfilled the criteria of MetS [27] as compared to 0% of the control group ($P = 0.001$). The very high prevalence of MetS among our patients could be explained by their relatively young age (mean 43.5 ± 3.7 years) and because all patients were selected to be obese. Regarding individual components of the MetS [27], the mean FBS in G1 was significantly higher than in controls ($P = 0.004$), although none of the patients was in the diabetic range. Also, significantly higher triglyceride levels and significantly lower HDL levels were seen in G1 ($P = 0.000$, each). In our study, a significantly negative correlation was found between the K–L grade and the HDL level ($r = -0.4$, $P = 0.02$).

Hyperuricemia is frequently observed in obese subjects due to the overproduction of uric acid and its impaired renal excretion [31]. Hyperuricemia predicts the development of hypertension, metabolic syndrome, diabetes, stroke, and cardiovascular events. Epidemiologic studies have also found that hyperuricemia is an independent risk factor for renal dysfunction in the normal population and in patients with hypertension, diabetes, and CKD [32]. In the present study, G1 patients had significantly higher serum uric acid levels ($P = 0.000$) than the control group.

According to the National Health and Nutrition Examination survey (NHANES III), the MetS is independently associated with CKD in the general population and in non-diabetic adults [33,34]. Studies in animals and in humans have shown that obesity is associated with elevated GFR and increased renal blood flow, i.e. hyperfiltration [35], however, not all studies have shown an increase in GFR and renal blood flow in obese

Table 4 Correlations among physical, clinical and laboratory parameters in G1with GFR, microalbuminuria and K–L grade.

Compared Parameter	GFR		Microalbuminuria		K–L grade	
	R	*P*-value	*R*	*P*-value	R	*P*-value
Disease duration	−0.3	0.1	0.5	0.02*	0.8	0.001*
WC	−0.1	0.6	0.3	0.1	0.4	0.005*
WHR	−0.2	0.1	0.3	0.08	0.1	0.4
WHtR	−0.2	0.3	0.4	0.03*	0.4	0.004*
BMI	−0.1	0.4	0.5	0.03*	0.5	0.001*
FBS	−0.1	0.6	0.1	0.6	0.1	0.5
TG	−0.2	0.2	0.2	0.2	0.2	0.2
HDL	0.4	0.02*	−0.4	0.02*	−0.4	0.02*
Microalbuminuria	−0.4	0.03*	–		–	
K–L grade	−0.4	0.03*	0.6	0.01*	–	

G1, group 1; WC, waist circumference; WHR, waist-hip ratio; WHtR, waist-height ratio; BMI, body mass index; FBS, fasting blood sugar; TG, triglycerides; HDL, high density lipoprotein; GFR, Glomerular filtration rate; ms, metabolic syndrome; K–L grade, Kellgren/Lawrence grade;
* $P < 0.05$ significant correlation.

individuals [36]. In the cross sectional study by Lo et al. conducted upon 380,207 individuals, a negative correlation between BMI and GFR was reported; being most evident in overweight and obese patients [37]. These controversies could be explained by the effect of the pattern of obesity on renal hemodynamics. An elevated BMI with central obesity results in increased intra-abdominal pressure from visceral fat deposition which may have several hemodynamic consequences, such as renal vein compression and may therefore raise renal venous pressure and diminish renal perfusion [38]. In the present study, all patients and controls had serum urea and creatinine within the normal laboratory reference ranges. None of the patients had hyperfiltration. Significantly lower GFR was found in G1 ($P = 0.001$), probably attributed to the very high prevalence of MetS among this group. According to the K/DOQI staging system [29], 55% and 10% of patients of G1 were classified as stage II and III CKD, respectively, while 30% of the control group were classified as class II CKD; $P = 0.01$. The GFR was significantly negatively correlated with microalbuminuria ($r = -0.4$, $P = 0.03$), which was expected while no correlation was found between the GFR and parameters of obesity among the patients. Obesity has also been associated with the progression of CKD [39] and by revising the expected annual reduction [yearly decline] in GFR we found it to be 0.69 mL/min/1.73 m^2/year in non-obese subjects using Tc-99 m DTPA [40]. In our study; the yearly decline in obese OA subjects was 1.65 ml/min using Tc-99 m DTPA that means approximately triple (exact ratio 2.75 the yearly GFR decline in non-obese subjects.

Microalbuminuria reflects widespread vascular damage and generalized vascular endothelial dysfunction. It is related to the interaction between components of the metabolic syndrome, particularly hypertension, insulin resistance and impaired glucose tolerance [41]. Indeed, microalbuminuria is considered as a component of the metabolic syndrome in the WHO definition [35]. This association between cardiovascular damage and low grade albuminuria is independent of renal function, and in the earliest stages of chronic kidney disease, low grade albuminuria seems to be a more important determinant than the glomerular filtration rate [42]. In the present study, G1 patients had significantly higher levels of microalbuminuria ($P = 0.008$). Microalbuminuria was significantly and positively correlated with BMI and WHtR ratio ($r = 0.5$ and 0.4, respectively; $P = 0.03$ each).

HDL is a risk factor for the development and progression of kidney dysfunction [37] and there was a significantly positive correlation in G1 between the HDL level and GFR in OA patients ($r = 0.4$, $P = 0.02$) as well as a negative correlation between the HDL level and microalbuminuria ($r = -0.4$, $P = 0.02$).

Due to the high prevalence of both cardiovascular risk factors and vascular comorbidity in OA it has been hypothesized that osteoarthritis or at least OA progression may be due to an atheromatous vascular disease of subchondral bone [43], it has even been questioned if osteoarthritis could be considered another component of the metabolic syndrome [14]. Recently, a large population – based study showed independent associations of atherosclerosis of the carotid arteries with osteoarthritis of the knee and hand joints in women [44]. Since microalbuminuria is a component of the metabolic syndrome of cardiovascular risk factors [35], microalbuminuria and osteoarthritis may represent different aspects of widespread vascular damage. This might explain the significantly negative correlation that was found in the present study between K–L stage of OA and GFR ($r = -0.4$, $P = 0.03$) and the significantly positive correlation between the duration of OA and K–L grade with the level of microalbuminuria ($r = 0.5$ and 0.6, $P = 0.02$ and 0.01, respectively).

At the end, we have to face our limitations as the relatively small number of involved subjects and not investigating the effect of food-intake habits [protein versus vegetarian style and salt intake habits] that were suggested recently to affect GFR [45]. Our study is preliminary. Further studies with larger numbers of subjects including normal weight patients with knee OA are needed to investigate the association between osteoarthritis and renal dysfunction.

In conclusion, middle-aged obese Egyptian patients with knee OA represent a high risk group for cardiovascular risk and renal dysfunction. Renal dysfunction is associated with the degree of obesity, low HDL level and with longer duration and increased severity of OA. Treating physicians should be cautious when describing non-steroidal anti-inflammatory drugs for these patients. Maintenance of a healthy life style to control body weight is strongly recommended.

Conflict of interest

The authors have nothing to disclose.

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